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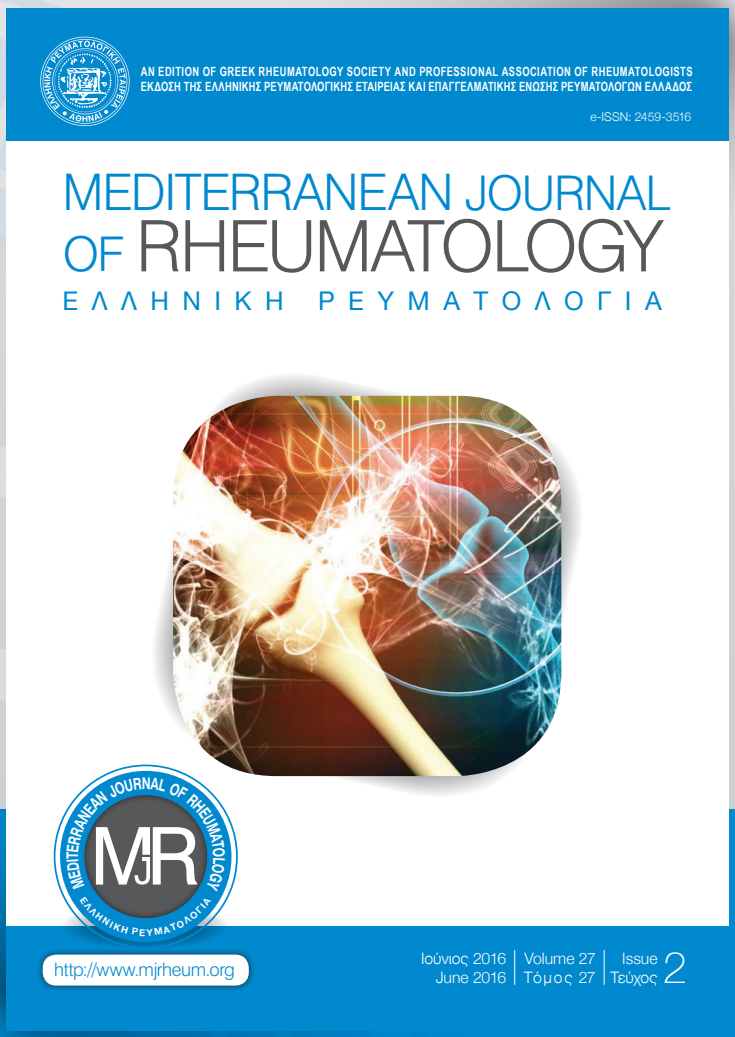

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EDITORIAL

How to reduce costs of biological treatments in patients with Rheumatoid Arthritis: The Dutch experience

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The management of Rheumatoid Arthritis (RA) has changed dramatically in the past decades. From "go low, go slow" with only a few Disease Modifying Anti-Rheumatic Drugs (DMARDs), currently in the management of RA terms like "intensive/aggressive, Treat to Target, Tight Control" are being used and applied. In addition, presently, more than 15 different treatment options are available ranging from conventional synthetic DMARDs (csDMARDs) costing a few hundred Euros annually, to biological DMARDs (bDMARDs), costing 10-15.000 Euros per patient per year. Recently, a targeted synthetic DMARD, the JAK kinase inhibitor tofacitinib, has been added to the armamentarium of the treatment of RA and many will follow in the coming years.

Many studies have shown the superior efficacy of the current strategy: less cumulative disease activity, less radiographic damage, less joint replacement surgery, better functionality, increased quality of life and more participation in the community.[1] In addition, as RA is a systemic disease, these benefits don't only apply to the joints. Since the new treatment strategies are being used, it appears that less comorbidities, for instance, less cardiovascular disease and fewer lymphomas, are being observed.

The downside of these new treatment strategies, mainly if bDMARDs are involved, are the costs. As health care professionals we are obliged to offer our patients the best possible, cost effective treatments. There are several ways to minimize the costs while keeping the benefits of these approaches. In the following, the experience from Dutch research and practice is discussed.

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TREAT TO TARGET STRATEGY WITH CONVENTIONAL SYNTHETIC DMARDS

Several remission induction studies have been performed in the Netherlands in the past decades: the BeSt (Behandel Strategieen) study, the COBRA (Dutch acronym: *Combinatie therapie Bij Rheumatoide Arthritis*; English translation: Combination Therapy For Rheumatoid Arthritis) study, the Camera (Computer-Assisted Management in Early Rheumatoid Arthritis) studies, DREAM (Dutch Rheumatoid Arthritis Monitoring) studies and the tReach (the Rotterdam Early Arthritis Cohort) study.[2-6] They have all shown that, with the combination of csDMARDs with dosages of methotrexate up to 25mg weekly - often given as a subcutaneous formulation - in combination with a short course of sometimes high dosages of corticosteroids, achieving remission is possible in a high percentage of patients. In those patients who are not responding enough, a biological DMARD can be added.

TAPERING OR STOPPING

The idea is that when the immune system has been down-regulated for a certain period due to treatment, it might be possible to stop the treatment without losing control of the disease. Already in 1996, it had been shown in a randomised study that in 50% of the patients who were in remission during csDMARD treatment, this treatment could be stopped without a flare of the disease.[7] Therefore, it was thought that, in patients in remission during treatment with biologicals as well, it should be possible to stop the treatment without losing disease control. In general, there are two ways of doing so: tapering by gradually decreasing the dose or increasing the dosing interval, or stopping right away. A theoretical disadvantage to tapering is the fact that the chance for antibody formation might be higher when the patients are treated for a longer period with subclinical dosages. This was the reason to perform a national

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stopping study in the Netherlands: the POEET (Potential Optimalisation of [Expendency] and Effectiveness of TNF-blockers) study.

a. Stopping

This was a randomised pragmatic study with 830 patients with RA who were in remission or low disease activity for at least 6 months.[8] A total of 47 centers in the Netherlands participated. It appeared that 50% of the patients remained in remission during at least 12 months after stopping the TNF inhibitor. In those patients restarting the TNF inhibitor because of a relapse, 80% achieved a state of remission or low disease activity in a short time period. In 20% of the patients, another treatment was needed.

b. Tapering

In a single center in the Netherlands, a tapering study was performed in 180 patients with RA who were on a stable dose of adalimumab or etanercept for at least 6 months and had low disease activity.[9] Patients were randomised between tapering (n=121) and usual care (59). Dose reduction occurred in 63% of the patients in the Tapering group and in 8% of the patients in the usual care group. There was no difference in flares between the two groups, although the cumulative disease activity and radiological progression was higher in the tapering group.

BIOSIMILARS

Recently, several biosimilars both for infliximab as well as for etanercept have been introduced. Randomised controlled studies have shown similarities with respect to efficacy and toxicity for these agents with the respective originals. The costs for these agents are about 30-40% lower than for the original product. Therefore, when starting a TNF inhibitor in a patient for the first time, it seems logical to start with the cheapest available option which might be a biosimilar. However, before we start substituting the originator for a biosimilar in patients already treated with a TNF inhibitor, we do need more studies showing that this is safe also on the long term. Data about this may arise from other countries, *e.g.* Norway, where substitution is already practiced in some health districts.

CONCLUSION

In a high percentage of patients with RA, remission can be achieved with csDMARDs. In case of insufficient response, adding biological DMARDs is an effective approach. When patients have reached a state of low disease activity or remission for at least 6 months, tapering or stopping the biological is a realistic option. Although we do not have long term data yet from a cost-effectiveness point of view, it is very attractive to stop or taper TNF inhibitors in patients who are on stable low disease activity or remission, as at least 50% of the patients will continue in their low disease activity state without biological treatment. Whether the interruption of the treatment in those patients that do experience a relapse leads to more joint destruction or to damage of extra-articular structures - like the cardiovascular system - is not known. Therefore, it would be very important to continue to monitor those patients in the long term.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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